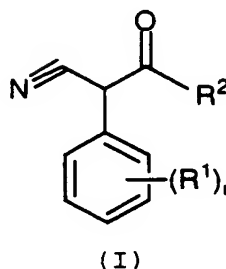


CLAIMS

What is claimed is:

1. A process for the preparation of a compound of
5 formula (I):



- 10 or a pharmaceutically acceptable salt form thereof;
wherein:
r is an integer from 0 to 4;
R¹ is independently selected at each occurrence from the group
consisting of:
15 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆
cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR^{1c}R^{1d}, -OR^{1e}, and -
SR^{1e};
R^{1c} and R^{1d} are independently selected at each occurrence from
the group consisting of:
20 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl;
alternatively, R^{1c} and R^{1d} are taken together to form a
heterocyclic ring selected from the group consisting of:
piperidine, pyrrolidine, piperazine, N-methylpiperazine,
25 morpholine and thiomorpholine, each heterocyclic ring
optionally substituted with 1-3 C₁-C₄ alkyl groups;
R^{1e} is independently selected at each occurrence from the group
consisting of:
H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆
30 cycloalkylalkyl;
R² is selected from the group consisting of:
H, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
cycloalkylalkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ haloalkyl, and
C₁-C₄ alkyl substituted with 0-5 R^{2a};

R^{2a} is independently selected at each occurrence from the group consisting of:

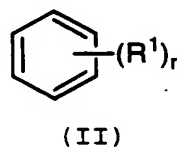
H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl, -OR^{2e}, and -SR^{2e}; and

R^{2e} is independently selected at each occurrence from the group consisting of:

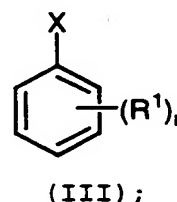
H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl;

the process comprising the steps of:

(1) contacting a compound of formula (II):

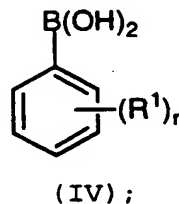


with a halogenating agent to form a compound of formula (III):

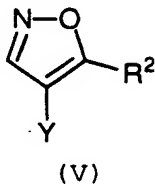


wherein X is a halogen derived from the halogenating agent;

(2) contacting the compound of formula (III) with a strong base followed by addition of an alkylborate to form a compound of formula (IV):

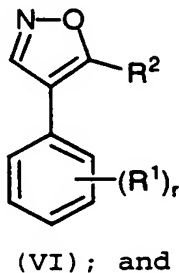


(3) contacting the compound of formula (IV) with a compound of formula (V):

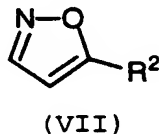


wherein Y is a second halogen;

in the presence of a catalyst and a weak base to form a compound of formula (VI):

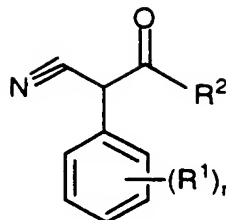


(4) contacting the compound of formula (VI) with an isomerization base to form a compound of formula (I), or a pharmaceutically acceptable salt form thereof; wherein the compound of formula (V) is prepared by contacting a compound of formula (VII):



with a second halogenating agent to give a compound of formula (V).

2. A process for the preparation of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt form thereof;

5 wherein:

r is an integer from 0 to 4;

R¹ is independently selected at each occurrence from the group consisting of:

10 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹ᶜR¹ᵈ, -OR¹ᵉ, and -SR¹ᵉ;

R¹ᶜ and R¹ᵈ are independently selected at each occurrence from the group consisting of:

15 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl;

alternatively, R¹ᶜ and R¹ᵈ are taken together to form a heterocyclic ring selected from the group consisting of:

20 piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C₁-C₄ alkyl groups;

R¹ᵉ is independently selected at each occurrence from the group consisting of:

H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl;

25 R² is selected from the group consisting of:

H, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkyl substituted with 0-5 R²ᵃ;

R²ᵃ is independently selected at each occurrence from the group consisting of:

30 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl, -OR²ᵉ, and -SR²ᵉ; and

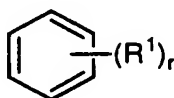
R²ᵉ is independently selected at each occurrence from the

group consisting of:

H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl;

5 the process comprising the steps of:

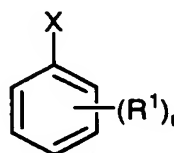
(1) contacting a compound of formula (II):



10

(II)

with a halogenating agent to form a compound of formula (III):

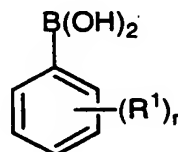


15

(III);

wherein X is a halogen derived from the halogenating agent;

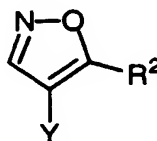
(2) contacting the compound of formula (III) with
20 a strong base followed by addition of an alkylborate to form a compound of formula (IV):



(IV);

25

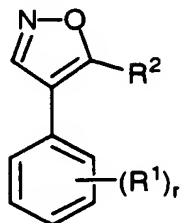
(3) contacting the compound of formula (IV) with a compound of formula (V):



(V)

wherein Y is a second halogen;

- 5 in the presence of a catalyst and a weak base to form a compound of formula (VI):

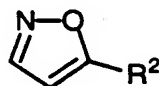


(VI); and

10

(4) contacting the compound of formula (VI) with an isomerization base to form a compound of formula (I), or a pharmaceutically acceptable salt form thereof;

- wherein the compound of formula (V) is prepared by
15 contacting a compound of formula (VII):

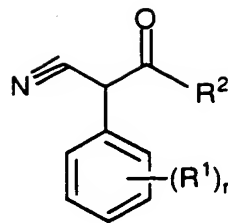


(VII)

- 20 with a halogenating agent in an organic acid to form a compound of formula (V).

3. The process of Claim 2, wherein R² is methyl, the halogenating agent is N-iodosuccinimide, and the organic acid is
25 trifluoroacetic acid.

4. A process for the preparation of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt form thereof;

5 wherein:

r is an integer from 0 to 4;

R¹ is independently selected at each occurrence from the group consisting of:

10 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹ᶜR¹ᵈ, -OR¹ᵉ, and -SR¹ᵉ;

R¹ᶜ and R¹ᵈ are independently selected at each occurrence from the group consisting of:

15 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl;

alternatively, R¹ᶜ and R¹ᵈ are taken together to form a heterocyclic ring selected from the group consisting of:

20 piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C₁-C₄ alkyl groups;

R¹ᵉ is selected from the group consisting of:

H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl;

R² is selected from the group consisting of:

25 H, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkyl substituted with 0-5 R²ᵃ;

R²ᵃ is independently selected at each occurrence from the group consisting of:

30 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl, -OR²ᵉ, and -SR²ᵉ; and

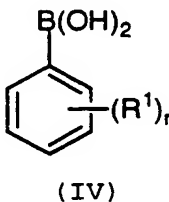
R²ᵉ is independently selected at each occurrence from the group consisting of:

H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl;

the process comprising the steps of:

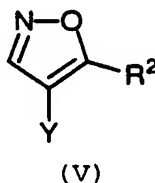
5

(1) contacting a compound of formula (IV):



10

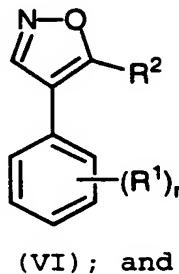
with a compound of formula (V):



15

wherein Y is a halogen;

in the presence of a catalyst and a weak base to give a compound of formula (VI):



20

(VI); and

(2) contacting the compound of formula (VI) with an isomerization base to give a compound of formula (I), or a pharmaceutically acceptable salt form thereof.

25

5. The process of Claim 4, wherein:

r is an integer from 0-3;

Y is iodine;

R¹ is independently selected at each occurrence from the group consisting of:

H, methyl and methoxy; and

5 R² is methyl.

6. The process of Claim 4, wherein:

in step 1, the weak base is sodium bicarbonate or a phosphate buffer with pH of about 7 to about 10,

10

the catalyst is tetrakis(triphenylphosphine)palladium(0) or [1,1'-Bis(diphenylphosphino)ferrocene] palladium (II) chloride; and

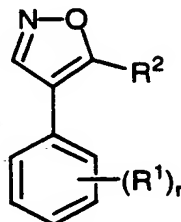
15 in step 2, the isomerization base is selected from the group consisting of:

lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, and
20 potassium tert-butoxide.

7. The process of Claim 4, wherein:

the weak base is sodium bicarbonate, the catalyst is [1,1'-Bis(diphenylphosphino)ferrocene] palladium (II) chloride, and
25 the isomerization base is sodium methoxide.

8. A process for the preparation of a compound of formula (VI):



30

(VI)

or a pharmaceutically acceptable salt form thereof;
wherein:

r is an integer from 0 to 4;

R¹ is independently selected at each occurrence from the group consisting of:

5 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR^{1c}R^{1d}, -OR^{1e}, and -SR^{1e};

R^{1c} and R^{1d} are independently selected at each occurrence from the group consisting of:

10 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl;

alternatively, R^{1c} and R^{1d} are taken together to form a heterocyclic ring selected from the group consisting of:

15 piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C₁-C₄ alkyl groups;

R^{1e} is selected from the group consisting of:

H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl;

R² is selected from the group consisting of:

20 H, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkyl substituted with 0-5 R^{2a};

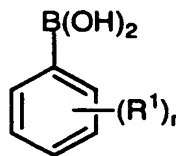
R^{2a} is independently selected at each occurrence from the group consisting of:

25 H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl, -OR^{2e}, and -SR^{2e}; and

R^{2e} is independently selected at each occurrence from the group consisting of:

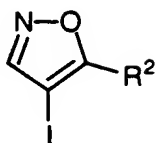
30 H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl;

the process comprising contacting a compound of formula (IV):



(IV)

with a compound of formula (V):



(V)

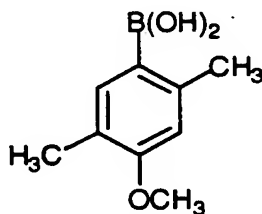
in the presence of [1,1'-Bis(diphenylphosphino)ferrocene] palladium (II) chloride, sodium bicarbonate and a suitable solvent to give a compound of formula (VI).

9. The process of Claim 8, wherein:

R² is methyl;

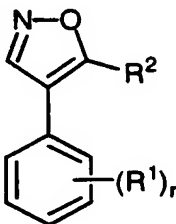
the suitable solvent is tert-butyl methyl ether; and

the compound of formula (IV) is:



(IV).

10. A compound of formula (VI):



(VI);

wherein:

r is an integer from 0 to 4;

R¹ is independently selected at each occurrence from the group consisting of:

H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR^{1c}R^{1d}, -OR^{1e}, and -SR^{1e};

R^{1c} and R^{1d} are independently selected at each occurrence from the group consisting of:

H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl;

alternatively, R^{1c} and R^{1d} are taken together to form a heterocyclic ring selected from the group consisting of:

piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C₁-C₄ alkyl groups;

R^{1e} is independently selected at each occurrence from the group consisting of:

H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl;

R² is selected from the group consisting of:

H, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkyl substituted with 0-5 R^{2a};

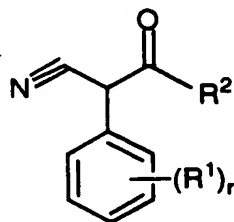
R^{2a} is independently selected at each occurrence from the group consisting of:

H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl, -OR^{2e}, and -SR^{2e}; and

R^{2e} is independently selected at each occurrence from the group consisting of:

H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆ cycloalkylalkyl.

11. A compound of formula (I):



(I)

wherein:

r is an integer from 0 to 4;

R¹ is independently selected at each occurrence from the group
5 consisting of:

H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆
cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR^{1c}R^{1d}, -OR^{1e}, and -
SR^{1e};

R^{1c} and R^{1d} are independently selected at each occurrence from
10 the group consisting of:

H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl;

alternatively, R^{1c} and R^{1d} are taken together to form a
heterocyclic ring selected from the group consisting of:

15 piperidine, pyrrolidine, piperazine, N-methylpiperazine,
morpholine and thiomorpholine, each heterocyclic ring
optionally substituted with 1-3 C₁-C₄ alkyl groups;

R^{1e} is independently selected at each occurrence from the group
consisting of:

20 H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆
cycloalkylalkyl;

R² is selected from the group consisting of:

H, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
cycloalkylalkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ haloalkyl, and
25 C₁-C₄ alkyl substituted with 0-5 R^{2a};

R^{2a} is independently selected at each occurrence from the group
consisting of:

H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆
cycloalkyl, C₄-C₁₂ cycloalkylalkyl, halo, CN,
30 C₁-C₄ haloalkyl, -OR^{2e}, and -SR^{2e}; and

R^{2e} is independently selected at each occurrence from the
group consisting of:

H, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, and C₄-C₆
cycloalkylalkyl.

35